Optical Relay Sensing of Cryptochiral Alcohols Displaying α-, β-, γ- and δ-Stereocenters or Chirality by Virtue of Isotopic Substitution

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Abstract: A reaction-based optical relay sensing strategy that enables accurate determination of the concentration and enantiomeric ratio (*er*) of challenging chiral alcohols exhibiting stereocenters at the α-, β-, γ- or even δ-position or hard-to-detect cryptochirality arising from H/D substitution is described. This unmatched application scope is achieved with a conceptually new sensing approach by which the alcohol moiety is replaced with an optimized achiral sulfonamide chromophore to minimize the distance between the covalently attached chiroptical reporter unit and the stereogenic center in the substrate. The result is a remarkably strong, red-shifted CD induction that increases linearly with the sample *er*. The CD sensing part of the tandem assay is seamlessly coupled to a redox reaction with a quinone molecule to generate a characteristic UV response that is independent of the enantiopurity of the alcohol and thus allows determination of the total analyte concentration. The robustness and utility of the CD/UV relay are further verified by chromatography-free asymmetric reaction analysis with small aliquots of crude product mixtures, paving the way toward high-throughput chiral compound screening workflows which is a highly sought-after goal in the pharmaceutical industry.

Introduction

The Mitsunobu reaction is among the most frequently used transformations in asymmetric synthesis.[1-3] It achieves high-yielding stereospecific conversion of a chiral alcohol to a new functional group with a variety of pronucleophiles in the presence of a phosphine and an azodicarboxylate. These readily available reagents work in tandem to generate a free nucleophile and a reactive alkoxyphosphonium salt, thus setting the stage for efficient one-pot functional group modification under mild conditions. The outstanding operational simplicity, click chemistry-like features and reliable inversion of the absolute configuration at the chiral carbon center have been instrumental in literally countless synthetic applications, in particular in total natural product synthesis. Since its introduction more than half a century ago,[4,5] the steadily increasing significance and popularity of the Mitsunobu reaction have inspired several mechanistic investigations[6,7] as well as innovative modifications and developments aimed at improving the synthetic value and scope.[8-11] By contrast, other potential uses of this powerful reaction have been largely neglected to date.

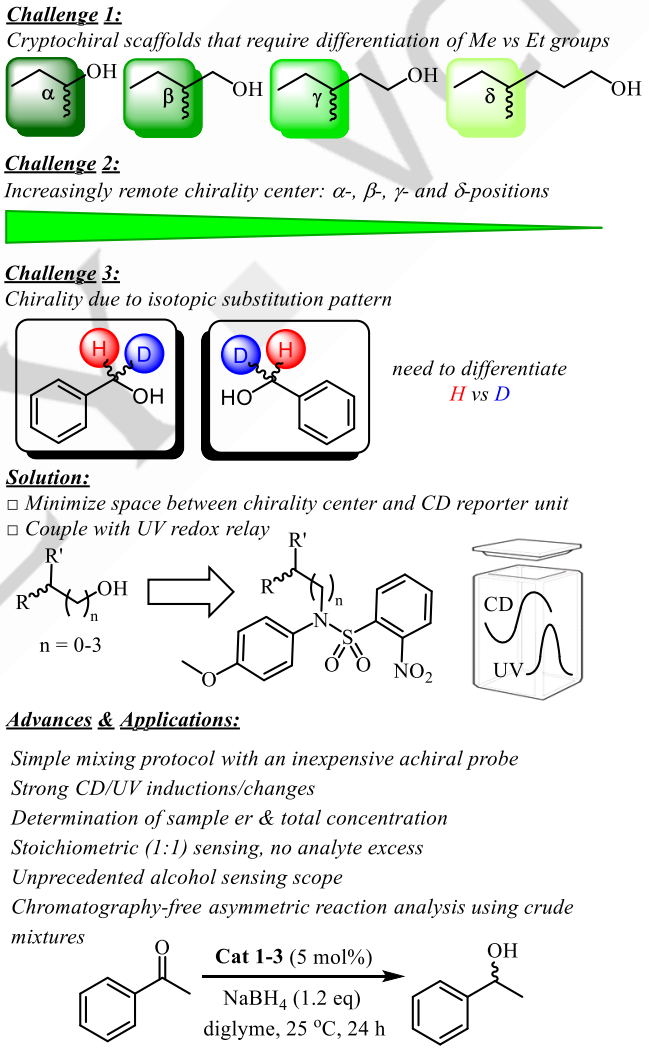


Figure 1. Chiroptical sensing challenges, advances and applications.

We envisioned that some of the privileged features of the Mitsunobu reaction could enable significant progress with chiroptical sensing of chiral alcohols. Optical analysis of the amount and enantiomeric composition of chiral compounds performed directly in mixtures without cumbersome chromatographic separation or other tedious work-up has received increasing attention in recent years.[12-22] This field has

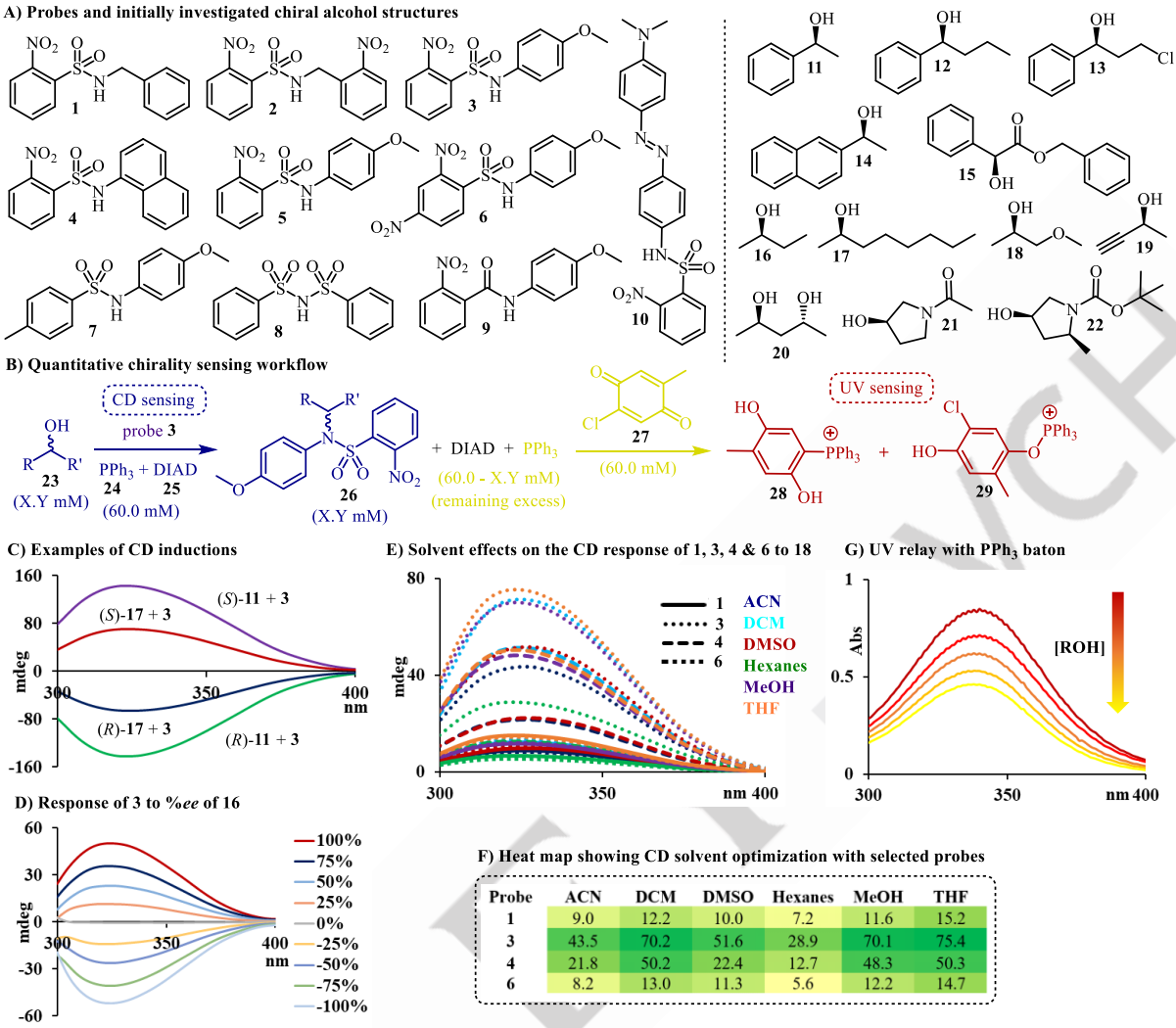
important applications across the chemical and health sciences, for example chromatography-free asymmetric reaction screening with crude mixtures or biomarker analysis, and bears huge promise to streamline numerous chiral compound development projects.[23] The state of the art of chirality sensing, however, is mostly confined to opportune compound classes like amines, amino alcohols, amino acids and α-hydroxy acids while alcohols have remained difficult.[24-39]

In most cases, chiral compounds exhibit weak, if any, blue-shifted circular dichroism (CD), UV or fluorescence signals that are insufficient for quantitative sensing purposes. This shortcoming can be easily addressed by introducing chromophoric probes through covalent bond formation or other means. The inherently weak nucleophilicity of alcohols, however, continues to hamper progress in this field and a practical method that is robust and broadly applicable but avoids harsh conditions, the use of unstable reagents, equilibria prone to side reactions and complicated sample processing is still elusive despite remarkable improvements in recent years.[40-45] To overcome these issues, we now repurpose the Mitsunobu reaction and apply it in a conceptually new sensing approach that, for the first time, does neither incorporate the alcohol into an acetal, carbamate or another functionality nor requires formation of a metal complex or supramolecular assembly but instead installs irreversibly and enantiospecifically an optimized sulfonamide chromophore directly at the chiral carbon center (Figure 1). We show that this new sensing strategy has several advantages. The ultimate contiguity of stereocenter and chromophore is conducive to strong CD inductions at long wavelengths which is a prerequisite for precise quantitative analysis and reduces the possibility of molecular interferences one might expect, for example, in multi-compound mixtures. Moreover, it enables sensing of very challenging chiral targets. Unmatched sensing scope and utility are demonstrated with alcohols having α-, β-, γ- or even δ-stereocenters and with an alcohol chiral by virtue of isotopic substitution. Notably, all these tasks become possible with a single probe and a unique CD/UV relay assay that exploits the Mitsunobu triphenylphosphine reagent in two ways: it mediates the chromophore placement directly at the chiral center to induce a strong CD signal and it also participates in a redox reaction with a quinone molecule to generate a characteristic UV response. This reaction sequence thus enables in-tandem determination of the enantiomeric ratio (*er*) and concentration of alcohol samples by using readily available chemicals that produce strong chiroptical signals at long wavelengths. The robustness of our reaction-based chiroptical assay is validated by accurate asymmetric reaction analysis with crude product mixtures. This eliminates the common need for chromatographic work-up and outperforms traditional workflows with superior speed while reducing workload and chemical waste production.

Results and Discussion

At the onset of this study, we decided to screen the sulfonamides, imides and amides **1**-**10** equipped with extended chromophores and nitro groups or other auxochromes expected to generate strong CD effects when covalently attached to the chiral target molecules via Mitsunobu reaction (Figure 2A and B). Note that all probes are achiral, an advantageous approach commonly favored in our laboratory to avoid formation of diastereoisomers produced when chiral sensors are used which can complicate the stereochemical analysis and result in systematic errors. By contrast, the reaction of **1**-**10** with a chiral alcohol preserves the original enantiomeric ratio (*er*) and we can use CD spectroscopy, inherently primed to differentiate between molecular mirror images, to determine *er* values directly from the intensity of the induced signals. We initially chose alcohols **11**-**22** as test compounds to develop and evaluate the sensing assay. This group includes 2-butanol, **16**, a particularly daunting sensing target that requires differentiation between a methyl and an ethyl group exhibiting very similar steric bulk at the chiral center. Importantly, direct sensing of free **11**-**22** is not possible because these compounds do not display quantifiable signals in the UV and CD regions of interest which are generally accepted to be above 300 nm where interferences from impurities or reagents and by-products expected in multi-compound samples such as crude asymmetric reaction mixtures can be more easily excluded. We found that several probes fulfill this criterion and generate CD signals located at approximately 325 nm. Moreover, **3** gave strong CD inductions with all alcohols tested indicating unmatched utility to address the long-standing shortcomings in the chiroptical sensing realm listed in Figure 1. Reaction monitoring by ^{1}H NMR spectroscopy and crystallographic analysis of an isolated product confirmed that the alcohol transformation conducted with **3**, PPh_3 and DIAD is quantitative and occurs with the expected configurational inversion (see SI). The induced CD (ICD) effects obtained with the enantiomers of 1-phenylethanol, **11**, and 2-octanol, **17**, are shown exemplarily in Figure 2C (see SI for chirality sensing of the other alcohols).

We then applied **3** to samples containing both enantiomers of 2-butanol in varying amounts, which revealed strong ICDs even with this challenging substrate and a linear relationship between the induced CD amplitude and the enantiomeric composition of **16** (Figure 2D and SI). The reaction is conveniently performed in acetonitrile/dichloromethane solution, but we found during our CD optimization studies that the choice of the diluting solvent, which is added prior to the optical measurements, is important (Figure 2E and SI). While several solvents can be used, the strongest ICDs were generally observed with probe **3** in either THF, MeOH or CH_2Cl_2 as shown in the corresponding heat map (Figure 2F). Having established a very sensitive chirality sensing protocol for alcohols, we decided to couple the CD assay with a complementary UV protocol to enable concomitant optical *er* and concentration analysis. In order to provide a user-friendly solution, we sought to integrate both tasks into a practical continuous workflow. We realized that this is possible by exploiting PPh_3 in two ways (Figure 2B). When used in excess it can assist stoichiometrically in the Mitsunobu reaction and also serve as relay baton to connect the *er* sensing chemistry with UV concentration analysis based on previously reported redox chemistry with quinones.[46,47] We discovered that this works very well with **27** yielding **28** and **29** as predicted by the literature and verified by ESI-MS analysis in our laboratory (see SI). Our chiroptical sensing relay thus produces a colorimetric change from red to yellow that is directly correlated to initial alcohol amount (Figure 2G). Importantly, the UV indicator **27** can be added directly into the CD sensing solutions and samples are then processed continuously after 5 minutes without any additional treatment.



Probe	ACN	DCM	DMSO	Hexanes	MeOH	THF
1	9.0	12.2	10.0	7.2	11.6	15.2
3	43.5	70.2	51.6	28.9	70.1	75.4
4	21.8	50.2	22.4	12.7	48.3	50.3
6	8.2	13.0	11.3	5.6	12.2	14.7

Figure 2. Assay components, chiral alcohol sensing concept and examples of CD and UV inductions. A) Structures of the probes and initially tested alcohols (only one enantiomer is shown for simplicity). B) Details of the CD/UV relay assay. C) Representative CD spectra obtained at 1.7 mM in THF. D) Linear CD amplitude increase as a function of sample %*ee*. E) Solvent screening of the CD sensing using alcohol **18** as test analyte. All spectra were collected at 1.7 mM. F) Heat map showing the probe performances in six different solvents. The increase in the CD amplitude is visualized using yellow (low) to green (high signal induction). G) The UV change obtained by consumption of surplus PPh_3 with quinone **27** is directly correlated to the initial alcohol concentration. See SI for details.

The performance of our relay assay was then evaluated with ten samples of 2-butanol covering a considerable range of total concentrations ([*S*]+[*R*]) and enantiomeric ratios ([*S*]/[*R*]) (Table 1). We were pleased to find that the chiroptical sensing method proved equally applicable to mixtures of small and large *er* values. For example, the analysis of a 35.0 mM sample consisting of 62.0% (*S*)- and 38.0% (*R*)-**16** gave 33.8 mM and an [*S*]/[*R*] ratio of 60.0:40.0 (entry 2). When a highly enantioenriched sample containing 8.0 mM of 2-butanol with an *er* of 98.0 (*S*):2.0 (*R*) was processed, the assay prediction was 7.5 mM with 98.5% (*S*)- and 1.5% (*R*)-**16** (entry 7). Generally, accurate quantitative analysis was achieved with an averaged absolute error for the concentration and enantiomeric composition determinations of +/- 1.5 mM and 1.3%, respectively. In addition, the absolute configuration of the major enantiomer was correctly assigned in each case based on comparison of the sign of the ICD signal with a reference sample.

Encouraged by the strong ICD effects produced by **3** with the challenging alcohols **16**-**19** where both alkyl groups exhibit similar steric bulk at the chirality center, we envisioned the possibility of chiroptical sensing of remote stereocenters. To the best of our knowledge, only one repo rt discussing chirality sensing of γ-stereocenters has appeared in the literature.[48] In this work, a widely applicable Anslyn metal coordination assembly was refined using new components that needed to be synthesized. While impressive proof-of-concept data were obtained, the assemblies consistently generated blue-shifted ICDs at low wavelengths below 300 nm which limits the suitability for real-world samples that would contain UV- or CD-active interferents. To overcome these shortcomings and to extend the sensing scope further we first processed **30**-**32** exhibiting a chirality center at the β-position. Again, strong CD effects were generated in all cases, prompting us to conduct a more systematic investigation (Figure 3).

Table 1: Results of the chiroptical sensing of samples of 2-butanol.

Entry	Sample composition			Sensing results		
	AC	Conc. (mM)	Ratio *S/R*	AC	Conc. (mM)	Ratio *S/R*
1	*S*	24.0	75.0:25.0	*S*	26.4	73.0:27.0
2	*S*	35.0	62.0:38.0	*S*	33.8	60.0:40.0
3	*R*	20.0	10.0:90.0	*R*	16.5	9.5:90.5
4	*R*	15.0	41.0:59.0	*R*	15.3	41.0:59.0
5	*S*	9.0	80.0:20.0	*S*	7.9	79.5:20.5
6	*R*	38.0	5.0:95.0	*R*	37.4	2.0:98.0
7	*S*	8.0	98.0:2.0	*S*	7.5	98.5:1.5
8	*S*	17.0	73.0:27.0	*S*	16.4	77.0:23.0
9	*S*	38.0	58.0:42.0	*S*	40.0	57.5:42.5
10	*R*	26.0	28.0:72.0	*R*	23.2	28.0:72.0

AC=Absolute configuration, Conc.=Concentration. See SI for details.

For this purpose, we returned to the aliphatic scaffold present in **16**. As mentioned above, stereodifferentiation between methyl and ethyl groups is a difficult task because of their very similar effective van der Waals radii, which is well documented by almost identical Taft and Charton steric parameters.[49,50] Compounds **33**-**35** systematically relocate the challenging *sec*-butyl unit in **16** into increasingly remote positions and display a growing degree of conformational flexibility, an additional obstacle that is generally detrimental to chiroptical sensing. Nevertheless, we were very pleased to find that remote sensing of this motif in **33**-**35** is possible with our reaction-based chiroptical assay (Figure 3 and SI). Altogether, the relatively simple probe **3** has a truly unique application scope and allows chirality sensing of alcohols with α-, β-, γ- or even δ-stereocenters.

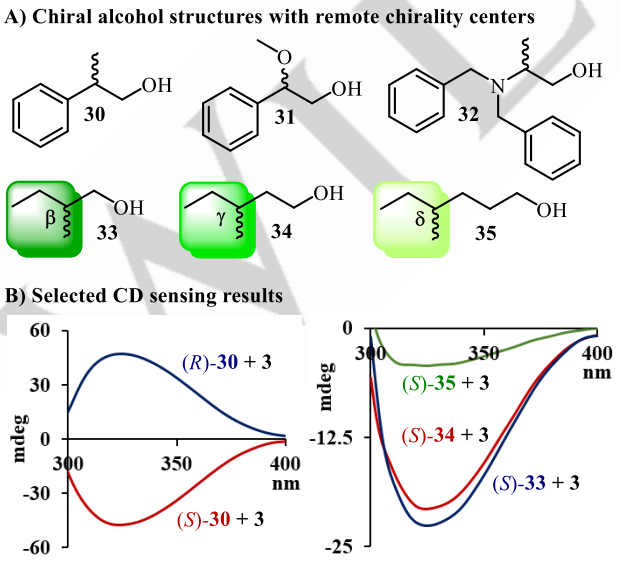


Figure 3. Remote chirality sensing. The CD spectra shown were obtained at 1.7 mM using THF as the diluting solvent.

Enantiodifferentiation between deuterated isotopomers by small-molecule CD probes is another longstanding goal in the sensing field. Since Maeda, Yashima and coworkers showed that this is possible through chiral amplification with 2,2'-biphenol-derived polyacetylene helices we decided to evaluate the utility of **3** for this task.[51] Following a modified literature protocol,[52] we prepared the enantiomers of **36**, which is chiral only by virtue of the H/D isotopic substitution at the benzylic position, via Ru-catalyzed asymmetric reduction of the corresponding aldehyde with formic acid-d_2 (see SI). In addition to the sensing of remote cryptochirality in **30**-**35** discussed above, our strategy to covalently place the optimized sulfonamide chromophore as close as possible or directly at the stereocenter as in **37** proves generally favorable for inducing quantifiable CD effects with these challenging molecules. As shown in Figure 4, probe **3** is perfectly suited for highly sensitive isotopic enantiodifferentiation of 4-bromophenylmethan-d-ol. We note that chiral HPLC,[53,54] NMR[55-58] using chiral media, vibrational CD[59] and chiral tagging in molecular rotational resonance (MRR)[60-64] spectroscopy are important techniques that have been applied to *er* and absolute configuration analysis of molecules exhibiting enantio- or diastereomeric H/D substitution patterns. In particular, MRR spectroscopy which requires gas-phase measurements and quantum chemical analysis of the transition frequencies seems well-suited for deuterated isotopomer analysis. Despite impressive advances in the last few years, enantioselective MRR analysis takes close to 10 minutes per sample[64] and is significantly more time-consuming than chiroptical sensing with automated CD plate readers which completes this task in only 3 seconds.[65] Moreover, MRR is limited to small molecules that are sufficiently volatile for the gas-phase experimentation. By contrast, our CD sensing method is not restricted to small molecules like **11**-**22** or **30**-**36** but also inherently applicable to large compounds like cholesterol, **38**, and the biologically active lignan podophyllotoxin, **39**, see SI.

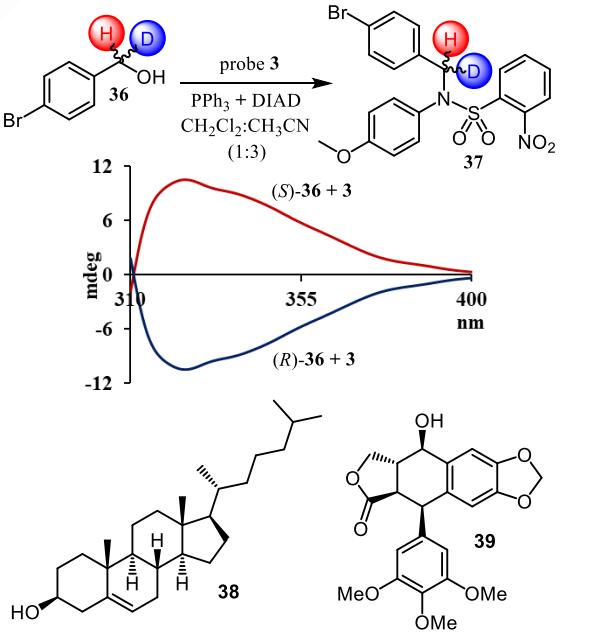
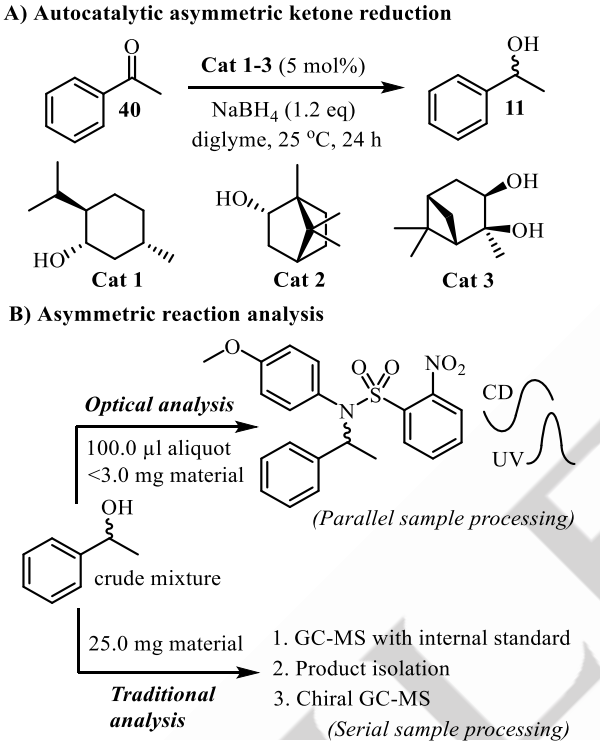


Figure 4. CD sensing of the enantiomers of **36** and structures of **38** and **39**. The CD spectra were obtained at 1.7 mM using THF as the diluting solvent. See SI for more information.

For comparison, we investigated the use of the well-known Mosher's acid and a chiral lanthanide shift reagent for enantioselective analysis of **33-36**, see SI. We observed that derivatization of alcohol **33** exhibiting a β-chirality center with Mosher's acyl chloride forms diastereomeric esters that have different ^{1}H NMR signatures but are only partially resolved in the ^{19}F NMR spectrum. However, attempts to resolve the ^{1}H and ^{19}F NMR signals of the diastereomeric esters formed with alcohols **34** and **35** having chirality centers in the γ- and δ-positions, respectively, failed. Similarly, insufficient ^{1}H and lack of ^{19}F NMR signal resolution were observed when we investigated the Mosher esters of the deuterated alcohol **36**. Attempts to use the chiral lanthanide shift reagent Eu(facam)$_3$ also proved unsuccessful due to low peak resolution and signal broadening which is consistent with literature reports with chiral alcohols.[66]



Cat	Traditional analysis			Chiroptical sensing		
	AC	Conv.	*S/R*	AC	Conv.	*S/R*
1	*S*	88.0	81.2:18.8	*S*	88.6	81.9:18.1
2	*S*	87.3	65.5:34.5	*S*	80.2	67.9:32.1
3	*Rac*	89.9	50.0:50.0	*Rac*	90.5	50.0:50.0

Figure 5. Asymmetric reaction analysis using traditional methods and chiroptical sensing. See SI for details. AC=Absolute configuration. Conv.=Conversion.

The ease of operation and unusual utility of our chiroptical relay sensing assay encouraged us to employ it without further adjustments in a real-world application with the goal to assess the robustness and general prospect of this methodology. Asymmetric reaction development generally requires screening of multiple parameters to identify optimal conditions that give the desired product in high yields and enantiomeric excess. The need to evaluate potentially synergistic effects of different catalysts, solvents, additives etc. on the reaction outcome under steadily increasing time constraints that chemists nowadays have to adhere to make it highly desirable to investigate hundreds of parameter combinations in parallel to cover a broad chemical space literally overnight. In principal, this is possible with today's high-throughput experimentation equipment but the widespread use of traditional analytical techniques that are serial in nature and time-consuming remains a serious bottleneck. We believe that this can be addressed with chromatography-free chiroptical determination of product yield and enantiopurity as CD microplate readers have recently become commercially available. This would, of course, necessitate chiroptical assays that are suitable for direct analysis of crude reaction mixtures. We therefore selected an autocatalytic asymmetric reaction[67] that gives a chiral alcohol and subjected a small portion of the product mixtures of three reactions run with different catalysts without any work-up and sample preparation to our UV/CD assay (Figure 5). Comparison with traditional GC methods showed that the conversion of **40** to **11** and the *er* of the chiral alcohol were determined with good accuracy and within an error range that is generally considered sufficient for high-throughput screening efforts aimed at rapid identification of optimal reaction conditions.

Conclusion

In summary, we have developed a practical reaction-based chiroptical sensing assay that allows simultaneous determination of the concentration and enantiomeric purity of an unprecedented range of chiral alcohols. This is achieved with a conceptually new CD/UV relay sensing strategy that does not use the alcohol moiety for binding to a sensor, which is the generally followed practice, but instead replaces it with an optimized chromophoric sulfonamide unit to minimize the distance between the covalently incorporated chiroptical reporter and the chirality center in the substrates. We demonstrate that this approach is conducive to strong CD and UV inductions at long wavelengths and enables enantiodifferentiation with very challenging targets exhibiting remote stereocenters or cryptochirality either by virtue of isotopic substitution or originating from sterically almost identical alkyl groups. The robustness and utility prospects of our sensing method were validated by chromatography-free asymmetric reaction analysis with small aliquots of crude product mixtures. This replaces the common need for elaborate sample work-up and inherently slow one-sample-at-a-time handling protocols with a broadly useful optical method that offers increased speed, parallel sample processing, small-scale analysis capability and reduced chemical waste production. Based on the recent introduction of commercially available multi-well UV/CD plate readers, we expect that this study paves the way toward high-throughput chiral compound development screening, a highly sought-after goal in the pharmaceutical industry where the synthesis of lead compounds often needs to be optimized by extensive reaction parameter optimization in a short time.

Experimental Section

All commercially available reagents and solvents were used without further purification. Reactions and sensing studies were carried out under anhydrous conditions. Experimental details, compound characterization data, NMR, ESI-MS, UV and CD

spectra, and crystallographic information are provided in the Supporting Information.

Acknowledgements

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Conflict of Interest

The authors declare no competing financial interest.

Keywords: Chiral alcohols • optical sensing • circular dichroism spectroscopy • cryptochirality • asymmetric reaction screening

[1] K. C. K. Swamy, N. N. B. Kumar, E. Balaraman, K. V. P. P. Kumar, *Chem. Rev.* **2009**, *109*, 2551-2651.
[2] S. Fletcher, *Org. Chem. Front.* **2015**, 2, 739-752.
[3] S. Munawar, A. F. Zahoor, S. Ali, S. Javed, M. Irfan, A. Irfan, K. Kotwica-Mojzych, M. Mojzych, *Molecules* **2022**, *27*, 6953.
[4] O. Mitsunobu, M. Yamada, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 935-939.
[5] O. Mitsunobu, M. T. Yamada, *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2380-2382.
[6] C. Ahn, R. Correia, P. DeShong, *J. Org. Chem.* **2002**, *67*, 1751-1753.
[7] S. Schenk, J. Weston, E. Anders, *J. Am. Chem. Soc.* **2005**, *127*, 12566-12576.
[8] T. Y. S. But, P. H. Toy, *J. Am. Chem. Soc.* **2006**, *128*, 9636–9637.
[9] D. Hirose, T. Taniguchi, H. Ishibashi, *Angew. Chem. Int. Ed.* **2013**, *52*, 4613-4617.
[10] J. A. Buonomo, C. C. Aldrich, *Angew. Chem. Int. Ed* **2015**, *54*, 13041-13044.
[11] Q. Guo, Y. Jiang, R. Zhu, W. Yang, P. Hu, *Angew. Chem. Int. Ed.* **2024**, *63*, e202402878.
[12] L. Pu, *Chem. Rev.* **2004**, *104*, 1687-1716.
[13] D. Leung, S. O. Kang, E. V. Anslyn, *Chem. Soc. Rev.* **2012**, *41*, 448-479.
[14] C. Wolf, K. W. Bentley, *Chem. Soc. Rev.* **2013**, *42*, 5408-5424.
[15] B. T. Herrera, S. L. Pilicer, E. V. Anslyn, L. A. Joyce, C. Wolf, *J. Am. Chem. Soc.* **2018**, *140*, 10385-10401.
[16] M. Quan, X.-Y. Pang, W. Jiang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202201258.
[17] J. S. S. K. Formen, J. R. Howard, E. V. Anslyn, C. Wolf, *Angew. Chem. Int. Ed.* **2024**, *63*, e202400767.
[18] B. T. Herrera, S. R. Moor, M. McVeigh, E. K. Roesner, F. Marini, E. V. Anslyn, *J. Am. Chem. Soc.* **2019**, *141*, 11151-11160.
[19] Z. A. De los Santos, S. MacAvaney, K. Russell, C. Wolf, *Angew. Chem. Int. Ed.* **2020**, *59*, 2440-2448.
[20] Y. Sasaki, S. Kojima, V. Hamedpour, R. Kubota, S.-y. Takizawa, I. Yoshikawa, H. Houjou, Y. Kubo, T. Minami, *Chem. Sci.* **2020**, *11*, 3790-3796.
[21] L. L. Wang, Z. Chen, W. E. Liu, H. Ke, S. H. Wang, W. Jiang, *J. Am. Chem. Soc.* **2017**, *139*, 8436-8439.
[22] D. S. Hassan, C. Wolf, *Nat. Comm.* **2021**, *12*, 6451.
[23] D. S. Hassan, F. S. Kariapper, C. C. Lynch, C. Wolf, *Synthesis* **2022**, *54*, 2527-2538.
[24] J. M. Dragna, G. Pescitelli, L. Tran, V. M. Lynch, E. V. Anslyn, *J. Am. Chem. Soc.* **2012**, *134*, 4398-4407.
[25] S. J. Wezenberg, G. Salassa, E. C. Escudero-Adan, J. Benet-Buchholz, A. W. Kleij, *Angew. Chem., Int. Ed.* **2011**, *50*, 713-716.
[26] H. Kim, S. M. So, C. P. Yen, E. Vinhato, A. J. Lough, J. I. Hong, H. J. Kim, J. Chin, *Angew. Chem. Int. Ed.* **2008**, *47*, 8657-8660.
[27] F. Biedermann, W. M. Nau, *Angew. Chem. Int. Ed.* **2014,** *53*, 5694-5699.
[28] Y.F. Wang, H. Yao, L.-P. Yang, M. Quan, W. Jiang, *Angew. Chem. Int. Ed.* **2022**, *61*, e202211853.
[29] L. L. Wang, M. Quan, T. L. Yang, Z. Chen, W. Jiang, *Angew. Chem. Int. Ed.* **2020**, *59*, 23817–23824.
[30] S. L. Pilicer, P. R. Bakhshi, K. W. Bentley, C. Wolf, *J. Am. Chem. Soc.* **2017**, *139*, 1758-1761.
[31] L. Joyce, E. Sherer, C. Welch, *Chem. Sci.* **2014**, *5*, 2855-2861.
[32] Z. A. De los Santos, C. C. Lynch, C. Wolf, *Angew. Chem. Int. Ed.* **2019**, *58*. 1198-1202.
[33] E. Badetti, K. Wurst, G. Licini, C. Zonta, *Chem. Eur. J.* **2016**, *22*, 6515-6518.
[34] P. Zardi, K. Wurst, G. Licini, C. Zonta, *J. Am. Chem. Soc.* **2017**, *139*, 15616-15619.
[35] H. Zhu, Q. Li, Z. Gao, H. Wang, B. Shi, Y. Wu, L. Shangguan, X. Hong, F. Wang, F. Huang, *Angew. Chem. Int. Ed.* **2020**, 59, 10868–10872.
[36] M. E. Shirbhate, S. Kwon, A. Song, S. Kim, D. Kim, H. Huang, Y. Kim, H. Lee, S.-J. Kim, M.-H. Baik, J. Yoon, K. M. Kim, *J. Am. Chem. Soc.* **2020**, *142*, 4975-4979.
[37] J. S. S. K. Formen, C. Wolf, *Angew. Chem. Int. Ed.* **2021**, *60*, 27031-27038.
[38] B. Li, J. Zhang, L. Li, G. A Chen, *Chem. Sci.* **2021**, *12*, 2504-2508.
[39] J. R. Howard, A. Bhakare, Z. Akhtar, C. Wolf, E. V. Anslyn, *J. Am. Chem. Soc.* **2022**, *144*, 17269–17276.
[40] L. You, J. S. Berman, E. V. Anslyn, *Nat. Chem.* **2011**, *3*, 943–948.
[41] L. You, G. Pescitelli, E. V. Anslyn, L. Di Bari, *J. Am. Chem. Soc.* **2012**, *134*, 7117–7125.
[42] C. Ni, D. Zha, H. Ye, Y. Hai, Y. Zhou. E. V. Anslyn, L. You, *Angew. Chem. Int. Ed.* **2018**, *57*, 1300–1305.
[43] F, Y. Thanzeel, B. Kaluvu, C. Wolf, *Angew. Chem. Int. Ed.* **2020**, *59*, 21382–21386.
[44] E. Nelson, J. S. S. K. Formen, C. Wolf, *Chem. Sci.* **2021**, *12*, 8784-8790.
[45] Z. A. De los Santos, C. C. Lynch, C. Wolf, *Chem. Eur. J.* **2022**, *28*, e202202028.
[46] F. Ramirez, S. Dershowitz, *J. Am. Chem. Soc.* **1956**, *78*, 5614–5622.
[47] S. I. Zhivetyeva, G. A. Selivanova, L. I. Goryunov, I. Yu. Bagryanskaya, V. Shteingarts, *J. Fluor. Chem.* **2015**, *180*, 21–32.
[48] J. J. Dotson, E. V. Anslyn, M. S. Sigman, *J. Am. Chem. Soc.* **2021**, *143*, 19187-19198.
[49] M. S. Sigman, J. J. Miller, *J. Org. Chem.* **2009**, *74*, 7633-7643.
[50] C.-Y. Lin, S. Lim, E. V. Anslyn, *J. Am. Chem. Soc.* **2016**, *138*, 8045-8047.
[51] K. Maeda, D. Hirose, N. Okoshi, K. Shimomura, Y. Wada, T. Ikai, S. Kanoh, E. Yashima, *J. Am. Chem. Soc.* **2018**, *140*, 3270–3276.
[52] I. Yamada, R. Noyori, *Org. Lett.* **2000**, *2*, 3425–3427.
[53] W. H. Pirkle, K. Z. Gan, *Tetrahedron: Asymmetry* **1997**, *8*, 811–814.
[54] K. Kimata, M. Kobayashi, K. Hosoya, T. Araki, N. Tanaka, *J. Am. Chem. Soc.* **1996**, *118*, 759–762.
[55] A. Meddour, I. Canet, A. Loewenstein, J. M. Pechine, J. Courtieu, *J. Am. Chem. Soc.* **1994**, *116*, 9652–9656.
[56] P. Lesot, O. Lafon, J. Courtieu, P. Berdagu, *Chem. Eur. J.* **2004**, *10*, 3741-3746.
[57] C. Naumann, P. W. Kuchel, *Anal. Chem.* **2015**, *87*, 10437–10442.
[58] J. Küppers, R. Rabus, H. Wilkes, J. Christoffers, *Eur. J. Org. Chem.* **2019**, 2629–2634.
[59] A. Masarwa, D. Gerbig, L. Oskar, A. Loewenstein, H. P. Reisenauer,P. Lesot, P. R. Schreiner, I. Marek, *Angew. Chem. Int. Ed.* **2015**, *54*, 13106 –13109.
[60] S. R. Domingos, C. Pérez, M. D. Marshall, H. O. Leung, M. Schnell, *Chem. Sci.* **2020**, *11*, 10863–10870.
[61] F. Xie, N. A.Seifert, W. Jäger, Y. Xu, *Angew. Chem., Int. Ed.* **2020**, *59*, 15703–15710.
[62] M. D. Mills, R. E. Sonstrom, Z. Pa Vang, J. L. Neill, H. N. Scolati, C. T. West, B. H. Pate, J. R. Clark, *Angew. Chem. Int. Ed.* **2022**, *61*, e202207275.
[63] Z. Pa Vang, R. E. Sonstrom, H. N. Scolati, J. R. Clark, B. H. Pate, *Chirality*, **2023**, *35*, 856–883.
[64] R. E. Sonstrom, Z. Pa Vang, H. N. Scolati, J. L. Neill, B. H. Pate, J. R. Clark, *Org. Process Res. Dev.* **2023**, *27*, 1185–1197.
[65] S. L. Pilicer, J. M. Dragna, A. Garland, C. J. Welch, E. V. Anslyn, C. Wolf, *J. Org. Chem.* **2020**, *85*, 10858–10864.
[66] M. Axt, J. Alifantes, V. E. U. Costa, *J. Chem. Soc., Perkin Trans. 2*, **1999**, 2783–2788.

[67] S. Chandrasekhar, R. Hota, *Tetrahedron: Asymmetry* **2005**, *16*, 751–754.

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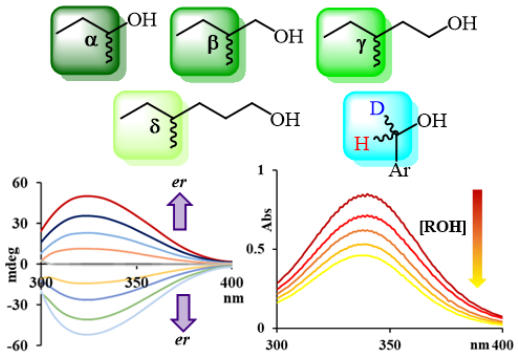

Sensing of chiral alcohols including chirality due to H/D substitution or remote asymmetry originating from similar alkyl groups has been a longstanding challenge. This is now possible with an optical relay assay that is based on a continuous Mitsunobu-quinone redox reaction sequence, generating strong CD and UV responses that correlate linearly to the enantiomeric excess and total amount. The value is demonstrated with chromatography-free asymmetric reaction analysis.